REMARKS

There have been no amendments to the specification or the claims. Claims 1-20 are pending in the application. Claims 1-8 and 15-20 were previously withdrawn, under traverse, from consideration based on a restriction of invention so that claims 9-14 are presently under consideration.

The restriction of claims 1-20 under 35 USC §121.

Claims 1-20 were previously alleged to represent five independent and distinct inventions restricted and were restricted into inventive Groups I-V. There was also a requirement to elect a single disclosed species for prosecution on the merits to which the claims would be restricted if no generic claim was finally held to be allowable. Claims 1, 6, 7, 9, 15 and 20 were admitted to be generic. During a telephone conversation with the Examiner Applicant provisionally elected, with traverse, Group III and the species of claim 13.

Group II includes claims 7-8. Claim 7 recites:

> A method of reducing the risk of neurodegeneration in a subject, comprising:
> administering to the subject a therapeutically effective amount of a lysosomal modulating compound, a physiologically acceptable salt of the lysosomal modulating compound, or a combination thereof, wherein enzymatic capacity of lysosomes in the subject is enhanced.

Group III includes claims 9-14. Claim 9 recites:

> A method for treating neurodegeneration in a subject, comprising:
> administering to the subject a therapeutically effective amount of a lysosomal modulating compound, a physiologically acceptable salt of the lysosomal modulating compound or a combination thereof, wherein enzymatic capacity of lysosomes in the subject is enhanced.

In order to strictly comply with the Examiner's requirement in the above restriction requirement, and without agreeing to the propriety of the restriction requirement, Applicant presently elects, with traverse, the invention of Group III, including claims 9-14 and the species of claim 13.

MPEP section 803 states (underlining added) "If the search and examination of an entire application can be made without serious burden, the Examiner must examine it on the merits, even though it includes claims to distinct or independent inventions."

The restriction requirement respectfully appears too restrictive in view of the claims of groups II and III. The Examiner has not shown it would be a "serious burden" to perform a complete search and examination on just claims 7-14 as originally filed. Alternatively, the Examiner has not shown it would be a "serious burden" to perform a complete search and examination on just Groups II and III. Since the Examiner has not made any showing of undue burden, each of the above requirements for restriction and election is respectfully traversed and the Examiner is respectfully urged to withdraw or modify the same.

The rejection of claims 9-14 under 35 U.S.C. §102(a or e) in view of U.S. Patent No. 6,458,760 to Seyfried et al.

Claims 9-4 were rejected under 35 U.S.C. §102(a or e) as having each and every feature and interrelationship anticipated by U.S. Patent No. 6,458,760 to Seyfried et al.

"It is elementary that an anticipation rejection requires a showing that each limitation of a claim must be found in a single reference, practice, or device." See In re Donohue, 226 USPQ 619, 621 point 2 (Fed. Cir. 1985).

Applicant's claim 9 recites in one pertinent part, with underlining added: "A method for treating neurodegeneration in a subject, comprising: administering to the subject a therapeutically effective amount of a lysosomal modulating compound . . . wherein enzymatic capacity of lysosomes in the subject is enhanced."

Applicant's specification shows that Z-Phe-Ala-diazomethylketone and related compounds can enhance cathepsin/lysosomal activity, doing so at concentrations lower than those needed for effective inhibition of cathepsins. In Applicant's specification this enhanced cathepsin/lysosomal activity was evident by the reduction in tau protein aggregates that are known substrates of cathepsin enzymes, and by increased levels of different cathepsin isoforms. The enhanced cathepsin levels corresponded with the

evident repair of neurodegeneration. Thus, Applicants method uses a therapeutically effective amount of a lysosomal modulating compound to ENHANCE the enzymatic capacity of lysosomes and thereby treat neurodegeneration.

The Seyfried reference lists Z-Phe-Ala-diazomethylketone with examples of cathepsin inhibitors, and teaches that the concentration of such compounds necessary to reduce ischemic cell damage matches that needed to inhibit the enzymatic activity. See, for example, with underlining added, column 3, lines 6-14: "Accordingly, the present invention is directed to treating tissue damage in a patient caused by ischemia comprising administering to said patient a therapeutically effective amount of a compound which is an inhibitor of at least one of cathepsin B or cathepsin L, wherein the inhibition of cathepsin B or L is significantly greater than that of calpain . . ."; column 3, lines 19-26: "The present invention is directed to a method for treating tissue damage in a mammal resulting from ischemia. The compounds useful for this purpose are small lipophilic molecules which are specific inhibitors of cathepsin B or cathepsin L or both."; column 7, lines 46-47: "The inhibitors used in the present invention are preferably compounds of Formula I described hereinabove."; column 13, lines 54-60: "The inventors have found that the peptidyl diazomethyl ketones described in the present application are specific inhibitors of cathepsin B or cathepsin L or both. In addition, they found that these are more effective in inhibiting these cysteine proteases than a compound which is a more general protease inhibitor. Moreover, the compounds used in the present invention are so specific that they do not substantially inhibit or block calpain and they are more effective inhibitors of cathepsin B or cathepsin L than calpain. The inhibitory effects and measurements thereof are described hereinbelow. "; column 17, lines 21-25: "The compounds of the present invention are inhibitors of very specific enzymes, viz., cathepsin B or cathepsin L or both."; column 19, line 67 to column 20, line 2: "Such ischemic cell damage is significantly reduced by the specific inhibitors of cathepsin B or cathepsin L utilized in the present method."; column 22, lines 10-12: "Without wishing to be bound, it is believed that the peptidyl diazomethyl ketones are effective because they inhibit cathepsin B or cathepsin L."; and claim 1: "A method of

treating tissue damage in a patient caused by ischemia comprising administering to said patient a therapeutically effective amount of a compound which is a specific inhibitor of either cathepsin B or cathepsin L . . .". See also example 6 which shows that their cathepsin inhibitor CP-1 reduces brain damage (infarct volume) at 10 micromolar (p=0.01) and even more of a reduction at 50 micromolar (p=0.003). This 50 micromolar concentration was also used to demonstrate that such a level of CP-1 also significantly reduced cathepsin B activity in example 9.

The method of U.S. Patent No. 6,458,760 to Seyfried et al uses a therapeutically effective amount of the recited compounds sufficient to INHIBIT enzymatic capacity of lysosomes. U.S. Patent No. 6,458,760 to Seyfried et al does not teach or suggest use of the compounds recited therein to enhance cathepsin/lysosomal activity and thereby treat neurodegeneration as taught and claimed in Applicant's invention. Applicant's claims 9-14 are patentable for at least this reason.

The rejection of claims 9-14 under 35 U.S.C. §103(a) in view of U.S. Patent No. 6,458,760 to Seyfried et al.

As stated in MPEP §2143, to establish a *prima facie* case of obviousness three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or combine the reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

As discussed above, U.S. Patent No. 6,458,760 to Seyfried et al does not teach or suggest use of the compounds recited therein to enhance cathepsin/lysosomal activity and thereby treat neurodegeneration as taught and claimed in Applicant's invention. Further, the teaching of the Seyfried reference that enzyme INHIBITION is necessary teaches away from Applicants claims 9-14. Applicant's claims 9-14 are not obvious over the Seyfried reference and are patentable for at least this reason.

The rejection of claims 9-14 under 35 U.S.C. §102(a or e) in view of document WO 00/56335 to Ellman et al.

Claims 9-4 were rejected under 35 U.S.C. §102(a or e) as having each and every feature and interrelationship anticipated by document WO 00/56335 to Ellman et al.

The Ellman application does not teach or suggest administering Z-Phe-Ala-diazomethylketone for treating neurodegeneration. The Ellman document merely uses Z-Phe-Ala-diazomethylketone (called ZPAD) at levels that inhibit cathepsin enzymes to induce pathogenic protein accumulation in order to show protective protein clearance with their claimed non-peptide aspartyl protease inhibitors (e.g., EA-1) as shown in Figures 11, 15A, and 16A. In fact, ZPAD treatment is shown to induce cellular accumulation of both tau species (see Figures 10A, 10C, 11, 14A, 14C, and 15A) and fragments of the amyloid precursor protein (Figures 10B and 10D). Accumulation of these protein species is well known to be associated with neurodegeneration. Since the Ellman document does not teach or suggest use of Z-Phe-Ala-diazomethylketone for treating neurodegeneration Applicant's claims 9-14 are patentable for at least this reason.

The Ellman document teaches methods to alter pathogenic events by administering a compound that inhibits aspartyl proteases including the lysosomal enzyme cathepsin D. See, for example with underlining added, page 3, line 2: "The present invention relates to (i) non-peptide aspartyl protease inhibitors; . . ."; page 5, lines 9-10: "In a particularly preferred embodiment, the aspartyl protease inhibitor is selected from . . ."; page 7, lines 1-3: "In yet another aspect, the present invention provides a method of treating a neurodegenerative disorder, the method comprising: administering to a mammal a therapeutically effective amount of an aspartyl protease inhibitor . . ."; page 15, lines 2-4: "The present invention relates to the identification of a number of small-molecule compounds which are capable of binding to and inhibiting aspartyl proteases and, in particular, cathepsin D . . ."; page 15, lines 17-20: "Thus, . . . non-peptidic compounds capable of inhibiting aspartyl proteases and, in particular, cathepsin D have now been identified."; page 29, lines 11-14: "The compounds of the

present invention have been found to be potent inhibitors of aspartyl proteases and, in particular, cathepsin D. As such, the present invention contemplates using the compounds of the present invention to inhibit cathepsin D, either *in vivo* or *in vitro*."; page 30, lines 23-25: "As explained above, the aspartyl protease inhibitors of the present invention modulate the processing of numerous proteins, such as amyloid precursor protein (APP), involved in diseases."; and claim 1: "A method for modulating the processing of an amyloid precursor protein (APP), said method comprising contacting a composition containing said APP with an aspartyl protease inhibitor . . .". The Ellman document does not teach or suggest use of the compounds recited therein to enhance cathepsin/lysosomal activity as taught and claimed in Applicant's invention. Applicant's claims 9-14 are patentable for at least this additional reason.

The rejection of claims 9-14 under 35 U.S.C. §103(a) in view of document WO 00/56335 to Ellman et al.

As stated above, the Ellman application does not teach or suggest administering Z-Phe-Ala-diazomethylketone for treating neurodegeneration. The Ellman document merely uses Z-Phe-Ala-diazomethylketone (called ZPAD) at levels that inhibit cathepsin enzymes to induce pathogenic protein accumulation in order to show protective protein clearance with their claimed non-peptide aspartyl protease inhibitors (e.g., EA-1) as shown in Figures 11, 15A, and 16A. In fact, ZPAD treatment is shown to induce cellular accumulation of both tau species (see Figures 10A, 10C, 11, 14A, 14C, and 15A) and fragments of the amyloid precursor protein (Figures 10B and 10D). Accumulation of these protein species is well known to be associated with neurodegeneration. Since the Ellman document does not teach or suggest use of Z-Phe-Ala-diazomethylketone for treating neurodegeneration Applicant's claims 9-14 are patentable for at least this reason.

Further, the Ellman document at page 58, lines 2-18 indicate that ZPAD causes "cultured slices to develop several characteristic features of the aged human brain". These teachings at page 58 and page 59, lines 12-14 of the Ellman document appear to

teach a person of ordinary skill in the art that ZPAD does NOT treat neurodegeneration but rather INITIATES neurodegeneration. This clearly teaches away from Applicant's claims 9-14. Applicant's claims 9-4 are not suggested by document WO 00/56335 to Ellman et al and are patentable for at least these additional reasons.

In summary, Applicants have addressed each of the rejections within the present Office Action. It is believed the application now stands in condition for allowance, and prompt favorable action thereon is respectfully solicited.

The Examiner is invited to telephone Applicant(s)' attorney if it is deemed that a telephone conversation will hasten prosecution of this application.

Respectfully submitted,

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